(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 397 689 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **11.05.94** (51) Int. Cl.5: **A61K 47/00**, //A61K31/045

(21) Application number: **89900785.0**

(22) Date of filing: **20.12.88**

(86) International application number:
PCT/AU88/00484

(87) International publication number:
WO 89/05659 (29.06.89 89/14)

(54) ORTHOSTATIC LAVAGE SOLUTIONS.

(30) Priority: **24.12.87 AU 6088/87**

(43) Date of publication of application:
22.11.90 Bulletin 90/47

(45) Publication of the grant of the patent:
11.05.94 Bulletin 94/19

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
WO-A-87/00754
WO-A-88/08715
AU-A- 8 813 063
AU-B- 8 173 343
AU-B- 8 430 504
FR-A- 2 336 922
US-A- 4 705 804

PATENT ABSTRACTS OF JAPAN, C-20; p. 338&NUM;

THE MERCK INDEX, 11th ed., 1989, Rahway, NY (US); pp. 130-131&NUM;

GASTROENTEROLOGY, vol. 78, 1980, American Gastroenterological Association; G.R. DAVIS et al., pp. 991-995&NUM;

GOODMAN & GILMAN's, "The Pharmacological Basis of Therapeutics", 7th ed., 1985, MacMillan Pub. Cie, New York, NY (US); pp. 997-998&NUM;

(73) Proprietor: **BORODY, Thomas Julius**
144 Great North Road
Five Dock, NSW 2046(AU)

(72) Inventor: **BORODY, Thomas Julius**
144 Great North Road
Five Dock, NSW 2046(AU)

(74) Representative: **Collier, Jeremy Austin Grey et al**
J.A.KEMP & CO.
14, South Square
Gray's Inn
London WC1R 5LX (GB)

EP 0 397 689 B1

Description

TECHNICAL FIELD

The present invention relates to orthostatic lavage solutions or colon evacuants for cleansing the gastrointestinal tract, or for treatment of bowel diseases and/or disorders.

BACKGROUND ART

Orthostatic lavage solutions or colon evacuants for cleansing the gastrointestinal tract were introduced into medical practice only within the last five years. The available solutions which seek to produce volumogenic diarrhoea by ingestion of relatively large volumes of electrolyte solution are almost all identical in their contents of salts, formulated so that they are relatively isotonic, and include poorly absorbable polyethylene glycol. Solutions which are commonly employed include 0.9% sodium chloride, balanced electrolyte solutions, lactated Ringers, mannitol and polyethylene glycol containing electrolyte solutions.

These solutions induce copious diarrhoea when the volume of the solution is greater than the bowel's capacity to distend and absorb it. Generally about 4 to 5 litre of the solution is necessary to obtain adequate cleansing of the gastrointestinal tract for colonoscopy or bowel surgery. Apart from the necessary diarrhoeagenic effect, the large volume required and the particularly unpleasant taste of the solutions contribute to the chief side effects of nausea and vomiting. These side effects are counter productive in reaching the desired aim of complete and rapid purging and cleansing of the bowel. The unpalatability of the solutions also result in poor patient compliance.

Flavouring the currently used solution with standard agents is difficult due to the large destabilizing amount of flavouring agents required to block the unpleasant nauseating taste of salts. Sugar based flavours are not acceptable since delivery of unabsorbed sugars to the colon provides a substrate for bacteria to elaborate explosive gases such as hydrogen and methane. In fact, recent studies (J. Crowe et al.[1]) have indicated that even the unflavoured polyethylene glycol solutions currently in use may create hydrogen and methane in potentially explosive concentrations when cautery is used within the colon.

Furthermore, most bowel Preparations using orthostatic lavage precede either colonoscopy or bowel surgery with a lesser usage in barium-enema bowel radiology. Since patients requiring such procedures are usually in the older age group and may be candidates for surgery after discovery of a bowel cancer, for example, it would be of advantage if the solution had bacteriocidal properties and/or could simultaneously replace nutrients necessary for repair.

Therefore it would be desirable to provide a colon evacuant wherein the unpleasant taste of the normally used isotonic solutions containing PEG is masked, wherein it has endogenous diarrhoea producing properties, and wherein it confers bacteriostatic of bacteriocidal properties to reduce bowel gas production or post-operative infection and yet can replace some nutrient value pre-operatively.

It is an object of the present invention to provide an agent which may be combined with flavouring and sweetening agents, which significantly reduces the potential for explosion due to a reduction of explosive gasses secondary to a bacteriostatic effect on bowel bacteria, and which allows a reduction in the volume of standard lavage solutions containing polyethylene glycol by at least about 25%.

Thus providing a more palatable and effective formulation, with fewer side effects, greater patient compliance and less risk of explosion.

DISCLOSURE OF THE INVENTION

The present invention provides a formulation for colon evacuation or for treatment of bowel diseases and/or disorders characterized in that it contains in solution ascorbic acid or a salt thereof in a concentration of 1 to 50 g/l, has an isotonic profile and contains high molecular weight polyethylene glycol. Because of the poor stability of ascorbic acid in solution, it should be packaged separately from the other components of the formulation or coated in dry formulations. In liquid formulations, it should not be added until just before use.

The formulations of the present invention may also contain electrolytes, for example, those having an isotonic profile. The formulations may also contain sweetening and/or flavouring agents.

If uncoated ascorbic acid is employed in the formulations of the invention it can cross react in the dry form with other components of the formulations.

The present inventor has found that the addition of ascorbic acid in larger than usual doses to typical lavage solutions tends to reduce the required volume for satisfactory colon evacuation. With the typical

polyethylene glycol electrolyte lavage solutions, the required volume for appropriate colon preparation is about 4 litre. The addition of ascorbic acid to the lavage solution has been shown to reduce the required volume to about 3 litre or less.

Using a formulation of the present invention, whole bowel irrigation may be carried out by administering a volume of about 2 to 3.5 litre of a lavage solution of the present invention over a period of time to induce volumogenic diarrhoea. Generally this period of time will be about 1.5 to 4 hours.

In the formulations of the present invention, ascorbic acid is incorporated in larger than usual oral concentrations to give a composition in the lavage solution of between 1 to 50 g/l, especially 1 to 25 g/l for colon evacuants or 20 to 35 g/l for treatment of bowel diseases and/or disorders. Since only a single dose is given during the lavage and the human intestine is capable of absorbing at most about 3 g of ascorbic acid (Hornig D. et al[2]), the remainder of the dose contributes to the diarrhoea and inhibits bacterial gas generation and reproduction. The excess ascorbic acid is passed without doing harm to the patient whilst the absorbed quantity is available as a specific nutrient and could be advantageous in the post-operative healing stage.

Typically, lavage solutions are provided in powdered form which are reconstituted to the required volume immediately prior to use. The lavage solutions of the present invention when made up ready for use will preferably contain from 5 to 50 g per 3 litre of solution when made up, more preferably about 20 g per 3 litre when made up.

For dry formulations the ascorbic acid must be coated. Silicone or ethyl cellulose form suitable coatings to prevent reaction between the ascorbic acid and other components of the formulation.

Suitable coated ascorbic acid is available from Roche Products Pty Ltd as Coated Ascorbic Acid, Type EC and Coated Ascorbic Acid, Type SC.

Lavage solutions of the present invention also contain high molecular weight polyethylene glycol such as polyethylene glycol having molecular weights greater than about 2000. Preferred polyethylene glycol has a molecular weight of about 3000 to 4500 such as PEG 3350, or PEG 4000.

Preferred lavage solutions of the present invention also contain a number of electrolytes and preferably have an isotonic electrolyte profile.

Preferred solutions have the following constituents in the range as specified.

	RANGE OF CONCENTRATION
	g/litre H_2O of made up solution
Polyethylene glycol	30 - 60
Sodium chloride	0.5 - 3.0
Potassium chloride	0.2 - 2.0
Sodium hydrogen carbonate	0.5 - 5.0
Sodium sulfate (anhydrous)	2.0 - 10.0
Ascorbic acid	1.0 - 50.0

Preferably, the polyethylene glycol in the standard lavage solutions is adjusted so as to result in an osmolality of approximately 289m osm/litre.

It is also possible to add flavourings to the lavage solutions of the present invention so long as these flavourings are not metabolized to an explosive gas such as hydrogen or methane in the bowel. For example aspartame may be added in a concentration of about 0.05 to 1%. Lemon flavour (SD - Natural lemon powder flavour No. 12606) or pineapple flavour (10966) may also be added at concentrations of 0.5 to 4.0% or cyclamates may be added to increase the palatability of the lavage solution.

The lavage solutions of the present invention are also useful in the treatment of certain gastrointestinal conditions such as small bowel bacterial overgrowth and irritable bowel syndrome as well as useful in treating acute or chronic bacterial bowel infections, for example, infection of the bowel with one or more bacteria including Campylobacter jejuni, Yersinia enterocolitica, Clostridium difficile, Cryptosporidium isospora belli. The lavage solutions of the present invention can also be used in the treatment of chronic inflammatory bowel disease such as Crohns disease or ulcerative colitis. In treating these conditions, ascorbic acid or its salts is used in a wide range of concentrations depending on the specific condition and may vary from 1 g to 50 g per litre, preferably from 20 g to 35 g per litre. Therefore, the lavage solutions useful in methods to treat the acute or chronic bacterial bowel infections or chronic inflammatory bowel disease will contain ascorbic acid or a salt thereof in a range so that when made up as ready for ingestion, the concentration of ascorbic acid will be from 1 to 50 g per litre. These lavage solutions useful in these

treatments will also be isotonic and include high molecular weight polyethylene glycol.

The invention will further be described by reference to the following examples.

EXAMPLE 1

A solution having the following composition was made up:

	g/l Water
Polyethylene glycol	54
Sodium chloride	1.46
Potassium chloride	0.745
Sodium hydrogen carbonate	1.68
Sodium sulfate	5.68
Ascorbic acid	6.6

A total of 3 litre was administered to the patient over 2 to 5 hours and the bowel preparation quality was found to be comparable to that requiring 4 litre of the standard available preparation. Ingestion was greatly facilitated due to the pleasant acidic taste which masked the usual nauseating taste of the salty polyethylene glycol solution. Colon hydrogen levels were acceptably low. Biopsies of colon obtained from the ascending transverse and descending colon sites were normal and without mucosal oedema.

EXAMPLE 2

A solution having the following composition was made up and administered as in Example 1.

	g/L Water
Polyethylene glycol	38
Sodium chloride	0.95
Potassium chloride	1.63
Sodium hydrogen carbonate	3.42
Sodium sulfate	2.75
Ascorbic acid	25
Lemon flavour	7.5

EXAMPLE 3

A solution having the following composition was made up and administered as in Example 1.

	g/L Water
Polyethylene glycol	49
Sodium chloride	2.4
Potassium chloride	1.2
Sodium hydrogen carbonate	2.82
Sodium sulfate	7.41
Ascorbic acid	37.1
Pineapple flavour	9.0

EXAMPLE 4

A solution having the following composition was made up and administered as in Example 1.

	g/L Water
Polyethylene glycol	57
Sodium chloride	2.7
Potassium chloride	1.8
Sodium hydrogen carbonate	4.45
Sodium sulfate	9.5
Ascorbic acid	46.5
Aspartame	9.0

EXAMPLE 5

A dry formulation having the following composition was made up:

Potassium chloride	2.092 Kg
Sodium chloride	4.127
Sodium hydrogen carbonate	4.748
Sodium sulphate (Anhydrous)	16.054
Ascorbic acid (Silicone coated)	16.959
Lemon flavour 12606	2.826
Aspartame	.565
Polyethylene glycol 4000	152.629
	Total 200.000

EXAMPLE 6

A dry formulation having the following composition was made up:

Potassium chloride	2.092 Kg
Sodium chloride	4.127
Sodium hydrogen carbonate	4.748
Sodium sulfate (Anhydrous)	16.054
Ascorbic acid (Silicone coated)	16.959
Pineapple flavour 10966	1.979
Aspartame	.565
Polyethylene glycol 4000	152.629
	Total 199.153

Individual doses of the dry formulations were made up to a volume of 3 litre with water, and the resultant solution was kept cold to increase palatability. The solution was administered to the patient over a period of 1 to 5 hours.

The formulation may be packaged for single applications in sachets, plastic bags or in a 3-4 litre jug to which water may be added to be made up to a specific volume. Alternatively the formulation may be packaged in screw top boxes or cartons, preferably with an air tight seal. Vitamin C can be kept separately in an air tight sachet to be added at the time of mixing particularly if it is uncoated by ethyl cellulose or silicone. It can also be packaged in sachets lined by agents such as Mylar to prevent water absorption.

REFERENCES

1. J. Crowe et al; A Study of Intracolonic Hydrogen and Methane Concentrations in Patients. GUT 1987; 28: A1370.
2. Hornig D. et al; Int. J. Vit. Nutry. Res. 1980; 50: 309.
3. WO-A-8 700 754

Claims

1. A formulation for colon evacuation or for treatment of bowel diseases and/or disorders characterised in that it contains in solution ascorbic acid or a salt thereof, in a concentration of 1 to 50g/l, has an isotonic profile and contains high molecular weight polyethylene glycol.

2. The formulation according to claim 1, wherein the concentration of ascorbic acid is about 20 to 35g/l.

3. The formulation according to claim 1 or 2, which contains at least one electrolyte.

4. The formulation according to claim 3, wherein the said electrolyte is selected from: sodium chloride, potassium chloride, sodium hydrogen carbonate, and sodium sulfate.

5. The formulation according to any one of claims 1 to 4, wherein the said polyethylene glycol has a molecular weight greater than about 2000.

6. The formulation according to claim 5, wherein the said polyethylene glycol has a molecular weight of about 3000 to 4500.

7. The formulation according to any one of claims 1 to 6, wherein the polyethylene glycol is present in an amount so as to result in an osmolality of about 289m osm/l.

8. The formulation according to any one of claims 1 to 7, further comprising a sweetening and/or flavouring agent not metabolized to an explosive gas.

9. The formulation according to claim 8, wherein said sweetening agent and/or flavouring agent is selected from: aspartame, pineapple flavour 10966, lemon flavour 12606 or cyclamates.

10. A formulation for colon evacuation or for treatment of bowel diseases and/or disorders, characterised in that it has the following composition: polyethylene glycol 30-60, sodium chloride 0.5-3.0, potassium chloride 0.2-2.0, sodium hydrogen carbonate 0.5-5.0, sodium sulfate (anhydrous) 2.0-10.0, ascorbic acid 1-50.0 g/l of water.

11. A formulation for colon evacuation or for treatment of bowel diseases and/or disorders, characterised in that it has the following composition: polyethylene glycol 54, sodium chloride 1.46, potassium chloride 0.745, sodium hydrogen carbonate 1.68, sodium sulfate (anhydrous) 5.68, ascorbic acid 6.6 g/l of water.

12. A dry formulation which, on dissolution in water, provides a formulation as claimed in claim 1 wherein the ascorbic acid is packaged separately from the other components or coated.

13. The formulation according to claim 12, wherein the ascorbic acid is coated with silicone or ethyl cellulose.

Patentansprüche

1. Formulierung zur Kolonentleerung oder zur Behandlung von Darmerkrankungen und/oder -störungen, dadurch gekennzeichnet, daß sie Ascorbinsäure oder ein Salz derselben in einer Konzentration von 1 bis 50 g/l in Lösung enthält, ein isotones Profil besitzt und Polyethylenglykol mit hohem Molekulargewicht enthält.

2. Formulierung gemäß Anspruch 1, in welcher die Ascorbinsäurekonzentration etwa 20 bis 35 g/l beträgt.

3. Formulierung gemäß Anspruch 1 oder 2, welche wenigstens einen Elektrolyten enthält.

4. Formulierung gemäß Anspruch 3, in welcher der Elektrolyt aus Natriumchlorid, Kaliumchlorid, Natriumhydrogencarbonat und Natriumsulfat ausgewählt ist.

5. Formulierung gemäß einem der Ansprüche 1 bis 4, in welcher das Polyethylenglykol ein größeres Molekulargewicht als etwa 2000 besitzt.

6. Formulierung gemäß Anspruch 5, in welcher das Polyethylenglykol ein Molekulargewicht von etwa 3000 bis 4500 besitzt.

7. Formulierung gemäß einem der Ansprüche 1 bis 6, in welcher das Polyethylenglykol in einer Menge vorliegt, daß sich daraus eine Osmolalität von etwa 289 m osm/l ergibt.

8. Formulierung gemäß einem der Ansprüche 1 bis 7, welche weiter einen Süß- und/oder Geschmacksstoff enthält, der nicht zu einem explosiven Gas verdaut wird.

9. Formulierung gemäß Anspruch 8, in welcher der Süß- und/oder Geschmacksstoff aus Aspartam, Ananasaroma 10966, Zitronenaroma 12606 oder Cyclamaten ausgewählt ist.

10. Formulierung zur Kolonentleerung oder zur Behandlung von Darmerkrankungen und/oder -störungen, dadurch gekennzeichnet, daß sie die folgende Zusammensetzung besitzt: Polyethylenglykol 30-60, Natriumchlorid 0,5-3,0, Kaliumchlorid 0,2-2,0, Natriumhydrogencarbonat 0,5-5,0, Natriumsulfat (wasserfrei) 2,0-10,0, Ascorbinsäure 1-50,0 g/l Wasser.

11. Formulierung zur Kolonentleerung oder zur Behandlung von Darmerkrankungen und/oder -störungen, dadurch gekennzeichnet, daß sie die folgende Zusammensetzung besitzt: Polyethylenglykol 54, Natriumchlorid 1,46, Kaliumchlorid 0,745, Natriumhydrogencarbonat 1,68, Natriumsulfat (wasserfrei) 5,68, Ascorbinsäure 6,6 g/l Wasser.

12. Trockene Formulierung, die beim Lösen in Wasser eine in Anspruch 1 beanspruchte Formulierung liefert, in welcher die Ascorbinsäure von den anderen Bestandteilen getrennt verpackt oder überzogen ist.

13. Formulierung gemäß Anspruch 12, in welcher die Ascorbinsäure mit Silikon oder Ethylcellulose überzogen ist.

Revendications

1. Formulation pour l'évacuation du contenu du côlon ou pour le traitement de maladies intestinales et/ou de troubles intestinaux, caractérisée en ce qu'elle contient une solution d'acide ascorbique ou d'un sel de celui-ci, à une concentration de 1 à 50 g/l, a des propriétés isotoniques et contient un polyéthylèneglycol de poids moléculaire élevé.

2. Formulation selon la revendication 1, dans laquelle la concentration de l'acide ascorbique est d'environ 20 à 35 g/l.

3. Formulation selon la revendication 1 ou 2, contenant au moins un électrolyte.

4. Formulation selon la revendication 3, dans laquelle ledit électrolyte est choisi dans l'ensemble constitué par le chlorure de sodium, le chlorure de potassium, l'hydrogénocarbonate de sodium et le sulfate de sodium.

5. Formulation selon l'une quelconque des revendications 1 à 4, dans laquelle ledit polyéthylèneglycol a un poids moléculaire supérieur à environ 2 000.

6. Formulation selon la revendication 5, dans laquelle ledit polyéthylèneglycol a un poids moléculaire d'environ 3 000 à 4 500.

7. Formulation selon l'une quelconque des revendications 1 à 6, dans laquelle le polyéthylèneglycol est présent en une quantité telle qu'on obtient une osmolalité valant environ 289 mosm/l.

8. Formulation selon l'une quelconque des revendications 1 à 7, comprenant, en outre, un agent édulcorant et/ou un agent aromatisant qui n'est pas métabolisé en un gaz explosif.

9. Formulation selon la revendication 8, dans laquelle ledit agent édulcorant et/ou agent aromatisant est choisi dans l'ensemble constitué par l'aspartame, l'arôme d'ananas 10966, l'arôme de citron 12606 et des cyclamates.

10. Formulation pour l'évacuation du contenu du côlon ou pour le traitement de maladies intestinales et/ou de troubles intestinaux, caractérisée en ce qu'elle a la composition suivante : polyéthylèneglycol 30-60, chlorure de sodium 0,5-3,0, chlorure de potassium 0,2-2,0, hydrogénocarbonate de sodium 0,5-5,0, sulfate de sodium (anhydre) 2,0-10,0, acide ascorbique 1-50,0, en grammes par litre d'eau.

11. Formulation pour l'évacuation du contenu du côlon ou pour le traitement de maladies intestinales et/ou de troubles intestinaux, caractérisée en ce qu'elle a la composition suivante : polyéthylèneglycol 54, chlorure de sodium 1,46, chlorure de potassium 0,745, hydrogénocarbonate de sodium 1,68, sulfate de sodium (anhydre) 5,68, acide ascorbique 6,6, en grammes par litre d'eau.

12. Formulation sèche qui, après dissolution dans de l'eau, fournit une formulation telle que revendiquée dans la revendication 1, l'acide ascorbique étant conditionné séparé des autres composants, ou enrobé.

13. Formulation selon la revendication 12, l'acide ascorbique étant enrobé de silicone ou d'éthylcellulose.